# Tetanus

## Prophylaxis and Treatment of the Disease

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• **Cleansing and debridement is paramount in dealing with tetanus-prone wounds (severe crushing injuries, piercing wounds, blisters and burns are outstanding examples, particularly if contaminated with dirt, grass or other debris).**

**Prophylaxis then is relatively easy in persons who have been actively immunized by toxoid injections. For them, a "booster" injection is indicated.**

**Use of antitoxin, however, is hazardous, whether for prophylaxis or for treatment of the disease. Since it may in itself cause severe disease, including anaphylactic reaction and serum sickness, decision to use it must be weighed against the possibility of the development of tetanus in each case.**

**To prepare for use of it, careful history should be taken, with particular reference to sensitivity to horse dander. Dermal tests, and perhaps ophthalmic tests, for sensitivity to the serum should be carried out. Even the tests may be hazardous and precautions should be taken accordingly.**

**If it is decided that the use of antitoxin is necessary even though the patient is sensitive to the material, desensitization must be carried out promptly, with adequate preparation for severe reaction.**

**There is experimental evidence that antibiotics of the tetracycline group, given soon after injury, may have prophylactic effect against tetanus.**

TETANUS IS SO HORRIBLE and terrifying a disease that the force of its impact is felt by the public and the medical profession alike.

Many phases of our understanding of tetanus are still controversial. One purpose of this article is to help clear the atmosphere and bring about a better understanding of prophylaxis and treatment of the disease. It is hoped also to stimulate physicians to urge public awareness that widespread inoculation with tetanus toxoid is a matter of great importance. The following data state the case cogently:

In California[10] from 1920 to 1954 there were 2,240 cases of tetanus in humans; 1,313 of the persons who had it died.

Tetanus developed in only one of 160,254 persons wounded in battle during World War II.[9] (A tetanus toxoid immunization program for all members of the armed forces was meticulously carried out.)

### BACTERIOLOGY AND PHYSIOPATHOLOGY

Clostridium tetani is a spore-bearing anaerobic bacillus. It is present in the intestinal tract of a large proportion of horses and cattle. About 5 per cent of all humans are carriers, but the proportion reaches 20 to 30 per cent among persons who are in close contact with animals.

In almost all cases of the disease the infection remains localized in the wound of entrance, although in rare cases the causative bacteria have been found in lymph nodes. Rarely does the organism enter the circulating blood.

The method of transport and action of the toxin is still a controversial subject. In 1903 Meyer and Ransome[11] concluded from their investigations that the toxin acted directly on the central nervous system, reaching it by way of the regional nerve trunks and spreading upward along the neural pathways in the spinal cord itself. Abel[1] conceded that the toxin may act locally on regional nerves and cause spasms of the muscles supplied by the affected nerves but contended that the toxin is distributed by absorption into the circulating blood.

The action of the toxin in selectively blocking inhibitory synapses in the central nervous system appears adequate to explain the phenomena of tetanus. Excitory impulses multiply and run through reflex pathways unchecked and uncoordinated to produce the muscular spasms so characteristic of the disease.

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### TETANUS-PRONE WOUNDS

Severe crushing injuries and compound fractures are outstanding examples of tetanus-prone wounds. This is particularly true if they are contaminated with dirt, grass and other debris. Often the organism develops in penetrating wounds, most frequently of all in wounds made by splinters; but even minor injuries such as blisters or pricks from rose thorns or needles are also frequent causes. Any burned surface is dangerous, for the bacillus of tetanus may be harbored under the blisters or encrustation.

Early and thorough treatment of the wound is most essential. No amount of antitoxin will prevent tetanus if dead tissue and foreign substances are

permitted to remain deep in the tissues. Wounds should be washed thoroughly with soap and water and copiously irrigated with saline solution. Penetrating wounds should be uncapped by removal of the superficial skin. Some wounds may be excised. All should be opened wide to facilitate removal of all dead tissues, blood clots and foreign bodies. If bone, tendons, vessels or nerves are exposed, they must be covered by sliding the skin over the wound or by skin grafting. Debridement and cleansing in these cases must be particularly meticulous.

## PROPHYLAXIS AGAINST TETANUS

The ideal prophylaxis against tetanus is active immunity brought about by injections of toxoid and sustained by periodic injections. Passive immunization—that is, the immunization or prophylaxis that is hoped for when antitoxin is given—entails considerable hazard and should be used only in situations of calculated risk. In some cases it might have to be foregone if the risk is too great.

The incidence of reactions to toxoid is 0.0237 per cent. Delayed serum sickness reactions to antitoxin occur in 30 to 40 per cent of patients.

### Active Immunization

Active immunization is accomplished by giving three tetanus toxoid injections of 0.5 cc. each, the second injection to be given 30 days after the first, and the third six months after the second.

To be effective, the course of toxoid inoculations must have been completed at least 30 days before the occurrence of the wound. Toxoid given at the time of injury to a patient who has not had a toxoid series of inoculations is without value. In no such circumstances can toxoid be a substitute for antitoxin.

Active immunization is particularly important for persons who are so sensitive to horse dander that contact brings on a severe asthma attack, because giving antitoxin to such a person, should the need occur, might be dangerous.

Basic immunity produced by a series of inoculations of toxoid declines with the passing of time. It is necessary, therefore, to give a booster injection every four to five years. It is interesting that following these subsequent doses, the blood antitoxin increases to a higher level than that produced by the primary two or three doses of toxoid.

The duration of the immunity so produced is unknown, but there is a growing conviction that it may last eight to ten years or even longer.

It should be borne in mind when treating a tetanus-prone wound that even naturally acquired immunity following recovery from an attack of tetanus is not lasting. Further, a prophylactic dose of tetanus antitoxin produces no lasting immunizing effect.

For children a trivalent vaccine—Diphtheria-Pertussis-Tetanus (DPT)—is recommended for the first five years of life; then the bivalent diphtheria-tetanus (regular) vaccine for ages six to eleven years and the diphtheria-tetanus (adult) vaccine for persons twelve years of age and over, with a booster injection every five years. Parents—and children, too, when old enough to remember—should be made aware that injections of toxoid are being given, should be firmly informed that booster doses are necessary and should be impressed with the importance of being able to inform another physician, should occasion arise, not only that immunization has been carried out but the date of the last booster.

The occurrence of tetanus in infants is alarming. In one recent year more than one-third of all deaths from tetanus in the United States occurred in patients less than one year of age. Immunization of the prospective mothers by toxoid would give a measure of protection to the newborn infant. Significant levels of antitoxin have been demonstrated in infants whose mothers previously received toxoid.[14]

### Passive Immunization

Since there is risk associated with the administration of a prophylactic dose of tetanus antitoxin, it is important to determine which wounds are such as to make the prophylactic use of antitoxin advisable. Obviously in the more serious cases antitoxin is almost mandatory, assuming, of course, that there has been no active immunization. The great problems are small wounds. The decision must be the physician's to make. In general, he may decide to withhold antitoxin in the case of a superficial wound that can be excised or adequately cleansed. If he decides that antitoxin is necessary, he should fully acquaint the patient with all the difficulties and risks of complications.

*Dosage of Antitoxin in Prophylaxis.* The usual dose of antitoxin given in prophylaxis has been 1,500 units. There is a distinct trend toward larger doses. Now 3,000 to 5,000 units is more generally acceptable. Many investigators now believe that in dealing with a patient who has a very severe, mutilating injury, a dose of 10,000 units or more is suitable. Using continuing doses of antitoxin daily or every other day until the danger is over is not considered proper for prophylaxis, since sensitization increases with each subsequent dose and tetanus would be more difficult to treat if it should occur.

Should a tetanus-prone wound be encountered several days after its occurrence, it still may not be too late for antitoxin, but a much larger dose of it—10,000 units at least—should be given.

#### *Prevention of Reactions to Antitoxin*

(a) *History of Allergic Tendencies.* It is essential to inquire carefully as to history of possible allergic sensitivity before giving any antitoxin. Most im-

portant is a history of asthma precipitated by contact with horse dander, for it is probable that the subject is highly sensitive to horse serum in any form and that administering antitoxin to him might be virtually impossible.

(b) *Tests for Sensitivity and for Reaction.* Before giving antitoxin, a test for sensitivity must be done. For this, an intradermal test and sometimes an ophthalmic test may be carried out.

For the average physician the intradermal test is the most practical. It is performed by injecting 0.02 cc. of 1:10 dilution of antitoxin intradermally. Using precisely that amount is important, for "readings" of reaction are unreliable otherwise. The same amount of normal saline solution is injected into the other arm as a control. The site of injection is kept under close observation for 15 to 20 minutes and if no local or constitutional reaction occurs, the result is "negative" and the required amount of antitoxin may be given subcutaneously with little fear of serious reaction.

Many authorities[2] believe that the ophthalmic test has a definite place in dealing with patients with a history of allergic disease. If the skin test for sensitivity to antitoxin is negative but there is history suspicious of allergic disease, the ophthalmic test is advisable. If the reaction to it is positive, it is a warning that any desensitization process or the administration of antitoxin may be hazardous.

The test is done by placing one minim of diluted horse serum (1:10 or 1:100) in the lower conjunctival sac of one eye and one minim of normal saline solution in the other. Lacrimation, redness and itching following the instillation of the horse serum, appearing immediately or 15 to 20 minutes later, are "positive" results; the absence of any of these manifestations is "negative."

The ophthalmic test is not without risk. Severe reaction may cause corneal injury and impairment of vision. To prevent this complication, epinephrine should be administered by dropping it into the eye (one drop of 1:1000 dilution) immediately upon the appearance of the first sign of severe reaction.

Rarely does a skin test show serious sensitivity reaction in a person with no history of hypersensitivity, and for such persons it is considered proper to perform the skin test in the average physician's office. Then, if there is no dermal reaction to the test, it is deemed relatively safe to administer the prophylactic serum subcutaneously. But if there is positive reaction, the patient must undergo a desensitization procedure.

#### Subcutaneous Desensitization and Prophylaxis

If there is a history of allergic disease in addition to the positive reaction to the test, desensitization is fraught with danger. To cope with any eventuality, the physician who carries out this work should have at hand a tourniquet, blood pressure apparatus, glucose and saline solutions for intravenous use, oxygen and mask and a tracheotomy set, epinephrine 1:1000 solution, Benadryl®, aminophylline and levarterenol bitartrate (Levophed®), nikethamide and agents for rapid digitalization. Unless all these facilities are readily available, the desensitization process had better be performed in a hospital where everything necessary is on hand and trained personnel is available.

If sensitivity to the antitoxin is demonstrated, further skin testing in series must be done, using successively more dilute solutions until one that causes no reaction is arrived at. That dilution is used as the basis for further desensitization procedures. Desensitization must be done with extreme care, particularly if the reaction to the first test was strongly positive.

A hypothetical example of the method follows:

The skin test is repeated until a dilution is reached at which no reaction was experienced. This dilution is, say, 1:1000. The desensitization then is carried forward, using this dilution for the first dose, then gradually increased doses at gradual increases in concentration as follows:

| Dilution: | |
|---|---|
| 1:1000 | 0.10 cc. if no reaction in 20 minutes |
| | 0.20 cc. " " " " " " |
| | 0.40 cc. " " " " " " |
| | 0.60 cc. " " " " " " |
| 1:100 | 0.10 cc. " " " " " " |
| | 0.20 cc. " " " " " " |
| | 0.40 cc. " " " " " " |
| | 0.60 cc. " " " " " " |
| 1:10 | 0.10 cc. " " " " " " |
| | 0.20 cc. " " " " " " |
| | 0.40 cc. " " " " " " |
| | 0.60 cc. " " " " " " |
| Concentrated serum | 0.10 cc. " " " " " " |
| | 0.20 cc. " " " " " " |
| | 0.40 cc. " " " " " " |
| | 0.60 cc. " " " " " " |

Administration is continued in this manner until 5,000 units had been given as a prophylactic dose.

In this desensitization procedure, if a local reaction develops such as a wheal or erythema at the site of the injection, the safest method is to go back one step and increase the dose more slowly, keeping it at dilutions that do not cause any local reaction.

Should any constitutional reaction appear—hives or generalized itching for example—and wheezing appear with it, the desensitization should be interrupted for intramuscular administration of 0.30 cc. of 1:1000 dilution of epinephrine and intravenous injection of 0.50 cc. of Benadryl® or Chlortrimeton® (5 to 10 mg.). It is advisable to wait 30 minutes

after the cessation of the symptoms of the constitutional reaction before continuing the desensitization, using half the dose that caused the reaction until the required amount of serum is given.

If anaphylactic shock is induced by the sensitization therapy, it must be vigorously treated in a manner described in a later section of this communication under Reactions to Antitoxin.

#### Intravenous Administration of Antitoxin

The intravenous administration of tetanus antitoxin is limited to the treatment of the disease and is not used for prophylaxis. Before giving antitoxin intravenously, it is mandatory not only to do a careful skin test (some physicians also use the ophthalmic test) but also to test further for sensitivity by giving small doses of antitoxin intravenously and carefully observing the result.

If the reaction to the preliminary skin test is negative, the intravenous test is done by diluting 0.5 cc. of antitoxin with 10 cc. of normal saline solution and injecting 0.5 cc. of this mixture as slowly as possible. If no signs of local reaction appear and there is no significant fall of blood pressure, the patient will usually tolerate the full required amount of the serum.

If there is a positive reaction to the skin test, it must be repeated in series, using successively greater dilutions of the serum until there is no dermal reaction. The final dilution that produced no dermal reaction is the basis for intravenous desensitization and administration. For example, assuming that the serum that produced no reaction was a dilution of 1:1000, the desensitization program is then begun by placing 1 cc. of this dilution in an infusion flask containing 100 cc. of normal saline solution, and this is given by slow intravenous drip. If no reaction develops in the first hour, further doses gradually increasing in strength are administered until the required amount is given. Should constitutional symptoms develop during the administration, the procedure must be stopped and these complications treated. Half an hour after cessation of the constitutional symptoms, the administration may be resumed, but with weaker dilutions, until the patient has received the required amount of antitoxin.

### REACTIONS TO ANTITOXIN

Most of immediate reactions are relatively mild, consisting of a wheal, erythema, induration and itching, and usually can be relieved by the oral administration of antihistamines or epinephrine 1:1000 given subcutaneously in a dosage of 0.2 to 0.3 cc.

Occasionally, asthma, wheezing and even edema of the larynx and lungs develop. These reactions are treated by epinephrine (0.3 to 0.5 cc. of 1:1000 dilution intramuscularly) and antihistamines (Chlortrimeton® 5 to 10 mg.) given intravenously. Aminophylline 0.25 gm. to 0.45 gm. in 20 cc. of saline solution infused by vein very slowly (8 to 10 minutes) may be helpful in relieving pulmonary symptoms.

*Severe Reactions of Anaphylactic Type.* Such reactions develop immediately. One of the early symptoms is a fall in blood pressure, and when this occurs the patient should be immediately placed in the Trendelenburg position.

Other symptoms that may be noted are general weakness, cough, wheezing and generalized itching and hives. Flushing of the skin soon gives way to pallor, cold and sweating. The first step in dealing with the emergency is to give 0.2 cc. of 1:1000 epinephrine at the site of the serum injection to slow the absorption by producing vasoconstriction. Epinephrine (0.3 to 0.5 cc. of 1:1000) is injected into the other arm at 15-minute intervals as indicated. In addition there may be need for administration of oxygen, phenylephrine (Neosynephrine®), levarterenol bitartrate (Levophed®), hypertonic glucose and rapid digitalization. Tracheotomy may be indicated.

*Delayed Serum Reactions.* Delayed serum reactions are those that do not occur until several hours after the serum administration, and usually they are not serious in character.

*Accelerated Serum Sickness.* Serum sickness may develop as early as 24 to 48 hours after administration of serum. The early appearance of symptoms often heralds a severe type of serum sickness.

*Late Serum Sickness.* The vast majority of cases of serum sickness fall into this category. Symptoms do not appear until 7 to 14 days after administration of antitoxin. Usually the symptoms are mild, consisting of hives and itching. Response to antihistamine therapy is usually prompt. But if the prodromal symptoms do not improve rapidly, they often become intensified and a serious type of serum sickness develops. Malaise, fever, adenopathy, angioneurotic edema of the lungs, pleuritis and pleural effusion may occur in addition to the local manifestations. Angioneurotic edema, hives and asthma usually can be relieved by giving 1:1000 epinephrine or 0.05 mg. of ephedrine. Respiratory difficulties can be lessened by intravenous administration of 0.25 to 0.50 gm. of aminophylline in 20 cc. of 5 per cent glucose solution. It is most important to give these agents very slowly. Steroid therapy is most effective for patients who do not respond to antihistamines. It may be begun by giving corticotropin (ACTH) 40 to 60 mg. intramuscularly or 10 mg. (in 1000 cc. of 5 per cent glucose solution) intra-

venously. Prednisone or prednisolone, 4 to 5 mg. three to four times daily, usually relieves the symptoms of the serum disease after a period of two to three days. Since side effects of such treatment are not unusual, the doses should be reduced as the symptoms diminish and discontinued as soon as they are fully abated. Steroids are contraindicated in the presence of active tuberculosis, but if treatment with them is decided upon as a calculated risk in such cases, double doses of antibiotics (500 mg. of Achromycin or Aureomycin four times a day) should be given at the same time. Diabetes is another contraindication, for diabetic coma may develop; and still another is duodenal ulcer, which may be aggravated by steroid therapy.

Generalized itching can be relieved occasionally by the use of procaine solution, 1.0 to 2.0 gm. in 500 to 1000 cc. of 5 per cent glucose by slow intravenous drip. Administration should be slowed or stopped if toxic symptoms such as hyperexcitability develop.

**Long Enduring Complications**

Fatal complications are rare, but do occur; and it must be recognized that disabilities following severe anaphylactic reactions and serum sickness may persist for a long time.

Neurologic complications occasionally accompany or follow a severe serum sickness. They vary widely from localized neuritis to generalized polyneuropathy.[12,13] The most common is brachial neuritis; and sciatic neuritis is not uncommon. Complications of this kind are often resistant to therapy for weeks, months or even longer.

**Substitutes for Horse Serum Antitoxin**

Bovine antitoxin produces the same complications as does horse serum in at least 75 per cent of cases. Moreover, it is not always readily available.

Despeciated horse serum* is available. Some of the "impurities" have been removed but the dangers of allergic sensitivities still exist.

Hog and sheep serum are not suitable substitutes.

**The Role of Antibiotics in Prophylaxis**

It has been shown conclusively that tetanus can be prevented almost always in animals by the use of antibiotics of one of the tetracycline group.[14] On the basis of these animal experiments, it is presumed that in humans, if a tetracycline is given intramuscularly shortly after injury in doses of 500 mg. every eight hours for three to five days, tetanus will not develop. There has not as yet been a sufficient number of humans treated in this manner to permit firm conclusions, but the data that is accumulating is encouraging.

*Treated with an enzyme to break down protein molecules.

**SYMPTOMS AND TREATMENT OF TETANUS**

The incubation period of tetanus may be no more than one day but the average is 14 days. Symptoms may occur within a day after the injury through which the organism entered. Early development of symptoms always presages a severe and dangerous course. The mortality is in inverse ratio to the time of onset. Since prompt treatment is important, the physician must be alert for the first signs of tetanus. Occasionally the first symptom is local twitching of the masseter muscle.

As soon as a diagnosis is made, the patient should be placed in a secluded, quiet and darkened room. Visitors should be banned, for any stimulus might bring about severe spasms or even convulsions. Trained nursing care is important and the patient should not be left alone.

The wound should be opened widely at once and debridement and irrigation carried out. Total excision of the wound is advisable where possible. Getting rid of the focus of infection is of utmost importance. This has been extended to amputation of a finger or even of a limb in cases of serious infection at the site of compound fracture. Bower[3] said that he had never known a patient in such circumstances to recover unless amputation was done.

Administration of tetanus antitoxin is the standard basic treatment for tetanus, for it is the only agent that will neutralize circulating toxin. It must be given as quickly as possible after the onset of symptoms to prevent the toxin's becoming fixed to nerve tissue. Tetanus toxin has been demonstrated in the circulating blood as long as 48 hours before the appearance of symptoms.

The initial dosage of antitoxin is somewhat controversial, but there is a very definite trend toward larger doses. It is the belief of the authors that at least 200,000 units should be given, half of the amount subcutaneously and the remainder, with caution, intravenously. Bower[3] said that the curative dose is somewhere between 160,000 and 350,000 units. Intraspinal administration is dangerous and has been abandoned.

The intravenous administration of tetanus antitoxin is fraught with danger. It must be borne in mind that the patient may have been sensitized by the prophylactic dose of antitoxin. Careful testing for sensitivity is mandatory, for a severe reaction may cause death. Since repeated doses may sensitize the patient, all serum should be given in the first 48 hours.

Sedative, anticonvulsant and muscle-relaxing agents are most helpful and are used routinely. The numbers and varieties of drugs that have been used are legion. Among these are bromides, amybarbital, chloral hydrate, various barbiturates, and procaine

(1 per cent) used intravenously. Morphine and meperidine are too depressing.

Recently, the best results have been obtained from the following: Tribromoethanol solution (60 to 80 mg. per kilogram of body weight); mephenesin; phenobarbital with mephenesin; mephenesin, barbiturates and chlorpromazine; calcium bromide and chloral hydrate.

Since respiratory complications are the direct cause of death in 80 per cent of fatal cases, a clear airway is important. Tracheotomy may be life saving.

Feeding the patient by the use of a Levine tube maintains the strength. Some observers have suggested gastrostomy but the authors consider this too drastic.

Use of penicillin to combat respiratory symptoms has reduced the mortality. Recently it has been suggested[4,14,15] that antibiotics of the tetracycline group are more specific and evidence is accumulating that they may be useful in human subjects. Florey[8] reported a case of tetanus in an infant who did not respond to antitoxin and penicillin. Chlortetracycline was then used and was credited with saving the life.

Blood transfusions may be of definite value, especially if the donors are known toxoid-immunized subjects, for blood from them may have a very definite specific effect.

It may be noted that when treating children with antibiotics, it is advisable to give, in addition, some gamma globulin, since there is a deficiency of this substance in the first year of life.

Corticosteroids have been tried in the more severe cases of tetanus[5] but they have not been proved to be useful and the authors look upon them with disfavor for the purpose, in light of the fact they are known to depress antibody formation.

## DISCUSSION

There are many differences of opinion as to methods of treating patients with tetanus. Some observers[6,7] believe that using epinephrine and Benadryl® in the same solution with the antitoxin will prevent reactions and aid absorption of the serum. The authors do not believe these methods are advisable, since they may obscure a dangerous reaction. Moreover, the drugs themselves may be poorly tolerated. Probably as many patients are hypersensitive to Benadryl® as to the serum itself.

Some investigators[2] emphasize the value of the ophthalmic test while others[3] declare it obsolete. The authors like and use the ophthalmic sensitivity test but the intradermal test is the basic one in use.

Bower[3] has expressed distrust of a negative reaction to a skin test for hypersensitivity and would rely rather on the blood pressure response. The authors believe the blood pressure is an important index but ought not exclude dermal tests.

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## REFERENCES

1. Abel, J. J., Firor, W. M., and Chalain, W.: Researches on tetanus. Further evidence to show that tetanus toxin is not carried to central neurons by way of the axis cylinders of motor nerves, Bulletin, Johns Hopkins Hosp., 53:373-403, 1938.

2. Alway, R. H.: Dean, School of Medicine, Stanford University, Stanford, Calif. Personal communication.

3. Bower, A.: Director of Contagious Disease Department, Los Angeles General Hospital. Personal communication.

4. Cecil, R. L., and Loeb, R. F.: Textbook of Medicine. W. B. Saunders, Publisher, 1955.

5. Chang, T. W., and Weinstein, L.: Effect of cortisone on treatment of tetanus antitoxin, Proceedings of Society for Exper. Biol. & Med., 94:431-433, Jan.-April 1957.

6. Christensen, N. A., and Thurber, D. L.: Clinical experience with tetanus, 91 cases, Proceedings of Staff Meetings of Mayo Clinic, Rochester, Minn., 32:156, April 3, 1957.

7. Christensen, N. A., and Stilwell, G. G.: Tetanus. A Present Day Analysis. World Medical Journal, W. B. Saunders Co., Publishers, Vol. 4, No. 1, Jan. 1957.

8. Florey, M. E.: Tetanus. The clinical application of antibiotics, Oxford, Publishers, 3:151, 1957.

9. Long, A. O., and Sartwell, P. E.: Tetanus in the United States Army in World War II, U. S. Army Medical Dept. Bulletin, 7:371, 1947.

10. Manual for the Control of Communicable Disease in California. Compiled by the California State Department of Public Health, 1956, p. 246.

11. Meyer, H., and Ransome, F.: Untersuchungen uber den Tetanus, Arch. Exper. Path. u Pharmakol., 49:369-416, July 2, 1903.

12. Poser, C. M.: Focal encephalopathy after administration of tetanus antitoxin, J.A.M.A., 164:871-873.

13. Rich, A. R.: Hypersensitivity in Disease. Harvey-Lecture, 1946-47. Charles C. Thomas, Publisher, Series 42, p. 106.

14. Stafford, E. S.: Discussing paper by Creech, O. Jr., Glover, A., and Ochsner, A.: Tetanus evaluation of treatment at Charity Hospital, Annals of Surgery, 146:382, Sept. 1957.

15. Taylor, W., and Novak, M.: Antibiotics and chemotherapy, 2:517-520, 1952.